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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/427,873	10/27/1999	MICHAEL R. BOYD	175912	3870

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EXAMINER

PARKIN, JEFFREY S

ART UNIT

PAPER NUMBER

1648

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/427,873	BOYD, MICHAEL R.
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## ***Office Action Summary***

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

1)  Responsive to communication(s) filed on 06 May 2002.

2a)  This action is **FINAL**.                    2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

4)  Claim(s) 20-27 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 20-27 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved.

12)  The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some \* c)  None of:

1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

\* See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

### Attachment(s)

15)  Notice of References Cited (PTO-892) 18)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_  
16)  Notice of Draftsperson's Patent Drawing Review (PTO-948) 19)  Notice of Informal Patent Application (PTO-152)  
17)  Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 20)  Other: \_\_\_\_\_

**Detailed Office Action**

***Continued Prosecution Application***

1. The request filed on 06 May, 2002, for a Continued Prosecution Application (CPA) under 37 C.F.R. § 1.53(d) based on parent Application No. 09/427,873 is acceptable and a CPA has been established. The communication accompanying this request was also  
5 considered. Applicant's representative is invited to contact the Examiner to schedule a telephonic interview.

***Status of the Claims***

2. The previously filed and unentered amendment dated 07 January,  
10 2002, has been entered. Claims 20 and 22 were amended in this response. Claims 20-27 are currently under consideration.

***35 U.S.C. § 112, First Paragraph***

3. The following is a quotation of the first paragraph of 35 U.S.C.  
15 § 112:

20 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25 4. Claims 20-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward therapeutic or prophylactic methods for inhibiting viral  
30 infection in a host through the administration of an antiviral protein, peptide, or conjugate thereof, having the amino acid sequence of SEQ ID NO.: 2, or a mutant thereof, wherein said

antiviral inhibits viral infection. The sequence of the antiviral molecule, SEQ ID NO.: 2, is derived from cyanovirin-N or CV-N. CV-N is a single 101 amino acid protein containing two intrachain disulfide bonds. The protein fails to display any significant sequence homology to other known proteins. It appears that CV-N binds directly to HIV-1 gp120. Other limitations specify that a viral envelope glycoprotein may also be administered with the antiviral peptide of interest. Applicant further indicates (see p. 4, specification) that "yet another object of the present invention is to provide a method of treating an animal, in particular a human, infected by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-2 [sic-HIV-1] or HIV-2. A related object of the present invention is to provide a method of treating an animal, in particular a human, to prevent infection by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2."

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure clearly fails to provide sufficient guidance pertaining to the molecular determinants modulating the antiviral activity of SEQ ID NO.: 2. Applicant contends that only routine

experimentation would be required to ascertain which peptides will work. The Examiner does not concur with this assessment. It has been well-documented in the prior art that single amino acid additions, substitutions, or deletions can have deleterious effects 5 on the activity of any given protein or peptide. Clearly the applicant does not understand which regions of CV-N are required for the antiviral activity. Applicant is reminded that the claims encompass any mutant of CV-N. This could include peptides with single or multiple amino acid additions, substitutions, or 10 deletions. Thus, the skilled artisan would be required to synthesize and screen an inordinate number of peptides. However, the disclosure clearly fails to direct the skilled artisan toward any particular portion of the CV-N peptide. The disclosure clearly fails to identify those portions of the CV-N peptide that are *sine* 15 *qua non* for the antiviral activity. Absent further guidance, the skilled artisan is being asked to guess as to which portions of the CV-N peptide can be manipulated.

2) The disclosure fails to provide sufficient guidance pertaining to the binding specificity of CV-N, or mutants, thereof. Applicant 20 provided declaratory data (06 August, 2001) illustrating that CV-N is also capable of binding to HSV-gC, both HIV-1 gp120 and gp41, and to a lesser extent, Ebola virus surface glycoprotein. However, the declaration fails to provide any guidance pertaining to the binding specificity of CV-N. It appears that CV-N binds to 25 oligosaccharides but no direction is provided pertaining to the specificity of the binding interaction. It is well-known in the art that viral envelope protein glycosylation patterns are quite variable. Thus, it is not readily manifest that all viruses will display the same affinity for CV-N. While it appears that CV-N binds to gp1-Z, gp120, and gp41 rather strongly, and sgpZ only 30 moderately, it is not clear that this binding interaction can be extended to all other viruses. Moreover, the disclosure and

declaration are both silent pertaining to acceptable amino acid additions, deletions, or substitutions that will result in the retention of antiviral activity in any given mutant.

3) The prior art teaches that the development of HIV-1 antivirals, 5 as well as other antivirals, has been a largely unsuccessful endeavor (Saunders, 1992; Wilting and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran et al., 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997) due to a 10 number of factors such as the lack of suitable animal models and the quasispecies nature of HIV. Applicant argues that the specification fully enables the claimed invention. It was argued that the *in vitro* assay relied upon is widely accepted as being predictive of *in vivo* and clinical results. Contrary to applicant's 15 assertion, the *in vitro* assay relied upon is clearly not a reliable predictor of clinical efficacy. It has been well-documented that simple *in vitro* screening assays are not predictive of clinical efficacy (Saunders, 1992; Wiltink and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran et al., 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997). As 20 Whittle and Blundell (1994) note, the rational design of antivirals is a difficult process. Random *in vitro* drug screening assays are only a rudimentary first step in the identification of efficacious antiviral agents. As the authors conclude, "while it [structure-based drug design] can be of great use in the initial process of 25 identifying ligands with improved affinity and selectivity *in vitro*, it can usually say very little about other essential aspects of the drug discovery process, e.g., the need to achieve an adequate pharmacokinetic profile and low toxicity *in vivo*." Accordingly, the results obtained from this assay do not constitute 30 an appropriate working embodiment. Thus, the *in vitro* tissue culture model relied upon is hardly predictive of clinical efficacy.

4) Applicant is reminded that the claims are also of excessive breadth. The claims broadly encompass methods of treating any viral infection and could include DNA viruses, RNA viruses, or retroviruses of vastly different genotypic compositions and 5 phenotypic activities. The claims encompass both enveloped and non-enveloped viruses. It seems quite improbable, considering the binding characteristics of CV-N, that it would maintain its antiviral activity toward non-enveloped viruses which clearly lack the determinants critical for binding. Moreover, the claims 10 broadly encompass methods that may employ various CV-N mutants. However, as noted *supra*, the disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the antiviral and binding activities of the cyanovirin. Absent such 15 guidance, the skilled artisan has only been extended an undue invitation to further experimentation.

5) It was previously argued that the disclosure failed to provide a sufficient number of working embodiments that would enable the full breadth of the claimed invention. Applicant contends that the specification is fully enabling and notes that data was obtained 20 from a macaque model. Applicant provided an earlier Declaration under 37 C.F.R. § 1.132 involving data obtained from an SIV model. A gel comprising CV-N was applied intrarectally or intravaginally and an inoculant comprising the virus SHIV89.6P administered. As 25 previously set forth, appropriately drafted claim language directed toward this embodiment would be acceptable. However, the SIV/SHIV model is not an accurate predictor of clinical efficacy (Rice and Bader, 1995). As Rice and Bader (1995) conclude, "the final test of a drug's efficacy comes in the clinical experience."

There were a number of other concerns pertaining to the 30 declaratory data earlier provided (05 February, 2001). The declaration failed to address a number of important issues. For instance, the declaration was silent pertaining to challenge studies involving different HIV-1 and -2 isolates, as well as,

other viral isolates (i.e., FIV, BIV, EIAV, CAEV, HSV, CMV, HTLV, etc.). Insufficient guidance was provided concerning the ability of CV-N to inactivate physiologically relevant concentrations of HIV-1, HIV-2, or other viruses. The declaration was also silent 5 pertaining to the pharmacological and therapeutic profile of CV-N. The experimental model employed failed to measure reductions in viral load. It has been well-documented that HIV-1-infected patients produce upwards of  $1 \times 10^{10}$  virions per day. It seems 10 unlikely that adequate concentrations of the CV-N protein can be maintained over sufficient periods of time to provide any meaningful effect. The experimental model employed did not provide any guidance pertaining to the pharmacological properties of the peptide. Many compounds fail to display clinical efficacy because 15 of pharmacological concerns (i.e., binding and inactivation by serum proteins, rapid clearance rate, poor circulating half-life, inability to target the tissue of interest [i.e., the lymphatic compartment]). However, none of these properties were addressed in the declaration. Thus, the skilled artisan cannot make an 20 meaningful deductions pertaining to the therapeutic properties of the antiviral composition. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice 25 the claimed invention.

Applicant provided another Declaration by Dr. Michael Boyd 25 (dated 30 January, 2002) filed pursuant to 37 C.F.R. § 1.132. This declaration disclosed the preparation of a small number of CV-N mutants. A series of site-directed mutants (Asn30Ala/Gln/Val, Pro51Gly, Asn30Ala:Pro51Gly, Asn30Gln:Pro51Gly:Ala71Thr) were prepared and their *in vitro* antiviral activities against HIV-1 30 assessed. Applicant contends that the mutants displayed essentially the same antiviral activity as wildtype CV-N. Perusal of the data indicates that the mutants displayed the same or better

activity against three (RoJo, Ba-L, ADA) of the tested isolates, but poorer activity against one (WeJo) of the tested isolates. While this preliminary data is promising, it still fails to clearly identify those molecular determinants modulating the antiviral 5 activity of CV-N. The declarant further argues that by utilizing the three-dimensional structure of CV-N, the skilled artisan could design suitable mutants with the desired activity. Once again, this simply represents an invitation to further undue experimentation since the applicant does not know which molecular 10 determinants are responsible for the antiviral activity of CV-N. Additional data was provided concerning the ability of CV-N to inhibit Ebola virus infection in a murine model. While this data is promising, once again the murine model of infection is hardly predictive of clinical efficacy. Moreover, there is no reason to 15 suspect that this activity would be present against non-enveloped viruses which lack the requisite carbohydrate structures required for binding.

***Obviousness-Type Double Patenting***

20 5. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 25 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

30 6. A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and © may be used to overcome an actual or provisional

rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a 5 terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

7. Claims 20 and 21 stand **provisionally** rejected under the 10 judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-24 of copending Application Serial No. 09/428,275. Applicants have indicated that this rejection will be addressed when allowable subject matter has been agreed upon.

15 ***Correspondence***

8. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 20 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax 25 number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

9. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 30 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any

inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.  
Patent Examiner  
Art Unit 1648

27 July, 2002